REMARKS

Applicant respectfully requests reconsideration. Claims 30-41, 70-74 and 80-83 were previously pending in this application. No amendments have been made. As a result, claims 30-41, 70-74 and 80-83 remain pending for examination. No new matter has been added.

Rejection Under 35 U.S.C. § 103

The Examiner maintained the rejection of claims 30-41, 70-74 and 80-83 under 35 U.S.C. § 103(a) as unpatentable over Fire et al. (WO 99/32619 A1, the "Fire PCT application") in view of Noren et al. (U.S. 5,691,140), Conkling et al. (U.S. 5,459,252) and Talkad et al. (J. Bacteriol. 135: 528-541, 1978). Applicant respectfully traverses the rejection.

The Examiner asserts that the invention disclosed in the Fire PCT application is supported in US 60/068562 (the "Fire provisional application"). As support, the Examiner cites passages from pages 7, 11, and 12 and claims 1, 14, 16 and 20. (Office Action at page 3.) Applicant respectfully disagrees with the characterization of the disclosure in the Fire provisional application, as is discussed in greater detail below.

The Examiner concedes that the Fire PCT application is deficient in elements of the claimed invention, which the Examiner alleges is only that the Fire provisional application does not disclose a vector structure having two promoters flanking a DNA sequence, but the Examiner asserts that the Noren et al. patent remedies the deficiency of the Fire PCT application. (Office Action at page 3.) The Examiner asserts that the Noren et al. patent discloses the structure and utility of using vector having two promoters flanking a DNA sequence, and that such a vector can be used to transcribe both strands of the DNA sequence. (Office Action at page 4.) Applicant respectfully disagrees with the Examiner's statements that Noren et al. teaches a

vector that is used for transcription of both strands of a DNA sequence and disagrees that the person of ordinary skill in the art would understand Noren et al. to teach this.

In the parent application (US 10/057,108) of the instant application, Applicant filed a Declaration of Dr. Erwin Sablon ("Sablon Declaration"), which specifically addressed, among other prior art, the teaching of the Noren et al. patent. Applicant provides the Sablon Declaration herewith for its statements regarding the Noren et al. patent and in support of the traversal of the obviousness rejection.

In his Declaration, Dr. Erwin Sablon stated that the Noren et al. patent describes multipurpose cloning vectors for *in vitro* generation of high specific-activity RNA probes. (See Sablon Declaration, ¶7.) These vectors contain a multiple cloning site flanked by two phage RNA polymerase promoters positioned to express either strand of a DNA molecule inserted in the multiple cloning site. (See Sablon Declaration, ¶7.) These flanking promoters can be the same or different, such as two T7 promoters or a T7 promoter at one side and a SP6 promoter at the other side. (See Sablon Declaration, ¶7.) This agrees with the description in the Noren et al. patent (see, for example, column 2, lines 14-28 and column 8, line 64 to column 9, line 25).

The vectors described in the Noren et al. patent are used to generate either sense or antisense transcripts from the same vector *in vitro*, using the appropriate phage RNA polymerase. (See Sablon Declaration, ¶8.) As stated by Dr. Sablon, in order to generate highly specific RNA probes, it is crucial that only one strand becomes transcribed. (See Sablon Declaration, ¶9.) Transcription of only one strand of the vector can be accomplished by one of two methods. First, the vector can be linearized with a particular restriction endonuclease that cuts between the insert and one of the flanking promoters in order to ensure transcription of only one strand. (See Sablon Declaration, ¶9.) This method is typically used when both flanking promoters are of the same type. (See Sablon Declaration, ¶9.) Second, only one promoter-specific phage RNA polymerase can be used in the *in vitro* transcription reaction. (See Sablon

Declaration, ¶9.) This method is typically used when the two flanking promoters are of different origin. (See Sablon Declaration, ¶9.)

In contrast to the vectors recited in the claimed invention, the vectors described in the Noren et al. patent "were clearly not intended to simultaneously produce transcripts from both directions." (See Sablon Declaration, ¶10.) Instead, the application describes, and the claims recite, the use of bidirectional expression vectors for *in vivo* generation in *E. coli* of double stranded RNA. (See Sablon Declaration, ¶11.) Dr. Sablon states that such a use would not have been suggested to the person of ordinary skill in the art by the Noren et al. patent for the reasons stated above. (See Sablon Declaration, ¶11.) Moreover, according to Dr. Sablon, bidirectional expression vectors that have opposite RNA polymerase promoters have been well known to, and universally used by, molecular biologists since the mid 1980s. (See Sablon Declaration, ¶11.) Notwithstanding the prior knowledge of the vectors in the art, Dr. Sablon states that the use of this type of vector even for *in vitro* production of both strands of double stranded (ds) RNA simultaneously, let alone *in vivo* production of dsRNA in a microorganism, was not even contemplated by any molecular biologist at that time, and in fact was not done until the present invention in the late 1990s. (See Sablon Declaration, ¶11.)

Therefore, the disclosure of the Noren et al. patent differs from the claimed invention in that it teaches *in vitro* and unidirectional transcription only, and does not describe a micro-organism comprising an expression vector with promoters flanking a DNA sequence such that the promoters initiate bidirectional transcription that would produce double stranded RNA in the micro-organism.

Moreover, according to Dr. Sablon, none of the documents cited by the Examiner, including in particular the Noren et al. patent, teach or suggest (alone or in combination) that one can express a double stranded RNA in a microorganism. (See Sablon Declaration, ¶16.)

Dr. Sablon states that his opinion is that a person of ordinary skill in the art would not have had a reasonable expectation of success of practicing the claimed invention based on the combination of references cited by the Examiner, which included the Noren et al. patent. (See Sablon Declaration, ¶17.) More specifically, Dr. Sablon stated that a person of ordinary skill in the art would not have had a reasonable expectation of success based on the combination of references cited by the Examiner of using the type of vectors known in the art (i.e., those of Noren et al. as cited by the Examiner) to express double stranded RNA inside a microorganism. (See Sablon Declaration, ¶17.)

Regarding the Examiner's characterization of the support for the Fire PCT application in the Fire provisional application, Applicant submits that the Examiner is reading too much into the text of the Fire provisional application after picking and choosing only sections that can be viewed as supporting the Examiner's rejection. However, when the Fire provisional application is read as a whole, as is required in prior art rejections, it is apparent that a person of skill in the art would not view the Fire provisional application as teaching the use of an expression vector that comprises promoters flanking a DNA sequence such that the promoters initiate transcription of said DNA sequence to produce double stranded RNA upon binding of a transcription factor to said promoters to produce double stranded RNA in a micro-organism.

The sections of the Fire provisional application referenced by the Examiner that disclose cells in fact describe cells containing the target gene, i.e., a *target cell*. These are not the same as the *micro-organism* claimed in the instant application. The same is true for the claims, which refer to inhibiting expression of a target gene in a cell by introducing a double stranded RNA into the cell (see claim 1).

Regarding the Examiner's statement on page 5 of the Office Action that "Fire et al. expressly taught that one can express double-stranded RNA in a cell of yeast or fungus" (emphasis added), Applicant respectfully disagrees and requests that the Examiner provide a citation to the Fire provisional application to support this statement. It appears, however, that the

Examiner may be referring to the same statements made on page 3 of the Office Action, which, as noted above, refers to a *target cell*, not a micro-organism.

The Examiner focuses on the description of transcription of RNA in the Fire provisional application. Transcription of RNA encoded by an expression vector was *generally* known in the art, but as stated by Dr. Sablon, the use of an expression vector for *in vitro* production of both strands of double stranded RNA (dsRNA) simultaneously, or for *in vivo* production of dsRNA in a microorganism, was not even contemplated at the time of the Fire provisional application. (See Sablon Declaration, ¶¶8-11.) Thus, it is clear that the references to transcription of RNA from vectors in the Fire provisional application is for transcription of individual strands separately using different vectors or expression systems configured to express one or the other strand, not together as is claimed in the instant claims.

Regarding the Examiner's selection of language from the claims of the Fire provisional application, Applicant submits that when read in the context of the Fire provisional application and the knowledge of the skilled person at that time (as stated by Dr. Sablon in his declaration), the claims of the Fire provisional application *do not support* the transcription of both strands of a double stranded RNA in a micro-organism, using an expression vector that comprises promoters flanking a DNA sequence such that the promoters initiate transcription of the DNA sequence to produce double stranded RNA upon binding of a transcription factor to the promoters.

The claims of the Fire provisional application recite that the double stranded RNA has one self-complementary strands (claim 13) or two separate strands (claim 14). For the two separate strands of claim 14, the claimed methods "further compris[e] synthesis of the two complementary strands" (claims 15 and 16) *and* "initiation of RNA duplex formation outside the cell' (claim 15) *or* "initiation of RNA duplex formation inside the cell" (claim 16). Thus the "inside the cell" emphasized by the Examiner relates to RNA duplex formation, not transcription of the RNA.

The Examiner states that the Fire provisional application teaches that "each" of the two strands of the double-stranded RNA can be synthesized and form a duplex inside a cell. Office Action at page 5. The Examiner then combines this general teaching with the teaching of Noren et al. that an expression vector allegedly can synthesize both strands of a double-stranded RNA and produce such a double-stranded RNA inside a cell. Applicant respectfully disagrees.

The Declaration of Dr. Sablon makes it clear that the vectors of the Noren et al. patent were not taught to be used to simultaneously express both strands of a nucleic acid molecule, and that a person of ordinary skill in the art at the time of filing of the application would not have expected simultaneous double strand synthesis to work. As such, the skilled person would not have had any reason to use the Noren et al. vectors in the Fire methods, and would not have had a reasonable expectation of success in doing so.

Therefore, Applicant submits that the combination of references cited by the Examiner does not provide all of the elements of the claimed invention and also fails to provide a person of ordinary skill in the art with a reasonable expectation of success of practicing the claimed invention, as required for a finding that the claims are obvious.

Accordingly, Applicant respectfully requests that the rejection of claims 30-41, 70-74 and 80-83 under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed payment, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Plaetinck et al., Applicant

By: /John R. Van Amsterdam/
John R. Van Amsterdam, Ph.D.
Reg. No. 40,212
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
Telephone: (617) 646-8000

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